REMARKS/ARGUMENTS

Rejection Under 35 USC 112, First Paragraph

Claim 46 has been rejected under 35 USC 112, first paragraph for lack of enablement. Claim 46 has been cancelled, thereby obviating this rejection.

Rejection under 35 USC 103(a)

Claims 37-45 have been rejected under 35 USC 103(a) as unpatentable over Gravina et al., and Solomon et al. in view of Shin et al., Friden, and Saito et al. More specifically, the Patent Office states:

> Gravina et al. teach that antibodies can be made against Aβ and Solomon et al. teach an antibody against Aβ has been made that will 'interfere with the aggregation of β-amyloid and trigger reversal to its nontoxic, normal components' (abstract). Shin et al. and Friden et al. teach that when an antibody to the transferrin receptor is fused to another antibody, uptake across the blood-brain barrier occurred. Saito et al. teach that when Aβ was conjugated to an antibody to the rat transferrin receptor, blood-brain barrier transport was increased. It would have been obvious...to produce a bispecific antibody that will cause the Aβ antibodies to be taken up across the blood-brain barrier.

Applicant respectfully traverses this rejection. None of the references teach or suggest synthesis of a bispecific antibody comprising a first antibody specificity which confers the ability of the bispecific antibody to cross the blood-brain barrier and a second antibody specificity conferring the ability of the bispecific antibody to bind to a β-amyloid epitope. Since none of the references exemplify synthesis of this bispecific antibody, none of the references could possibly teach that such a bispecific antibody would have the ability to cross the blood-brain barrier. As such, one of skill in the art would not be able to deduce from the teachings of the combination of Gravina et al., Solomon et al., Shin et al., Friden, and Saito et al. that a bispecific antibody of Applicant's Claims 37-45 would be able to cross the blood-brain barrier with any degree of

certainty. The teaching of a bispecific antibody comprising a second antibody specificity conferring the ability of the bispecific antibody to bind a β–amyloid epitope is lacking in the combination of cited references, and the combination of references cited does not cure this deficiency. Prior to Applicant's invention, one of skill in the art would not have been able to predict with any degree of certainty that an antibody to a β-amyloid epitope, in bispecific or other form, could cross the blood-brain barrier and retain its binding specificity. Results from experiments presented in the Exemplification section of Applicant's specification indicate, for the first time, that a bispecific antibody comprising an antibody specificity conferring the ability of the bispecific antibody to bind a β–amyloid epitope does, in fact, retain its amyloid specificity and is deliverable across the blood-brain barrier into the brain parenchyma and brain capillarities of a live animal when administered intravenously (pages 45-49 of Specification, Tables 10 and 11). As noted in the Specification, significant levels of labeled bispecific antibody probes of the present invention were found in the brains of mice treated with the transferrin receptor reactive bispecific antibody versus those receiving the control bispecific antibody (pages 48-49 of Specification, under Monitoring the Brain Distribution of Bispecific Antibody in Live Mice), a result the combined teachings of the references could not have predicted with any certainty.

The Patent Office, in citing Applicant's Amendment filed on 1/9/04, further states in support of this rejection:

> Applicant has admitted in their Remarks section that the production of such bispecific antibodies are 'well known in the art, and as such the production of the same is a matter of routine experimentation.'

For clarification, the actual quote from Applicant's Amendment appears below:

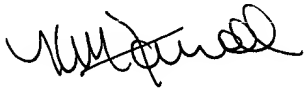
> The production of bispecific antibodies are well known in the art, and as such the production of the same is a matter of routine experimentation.

In the context of the Amendment, the above quote represents the state of the art at the time the Application was filed. Applicant's reference to the state of the art is in the context of the **production** of bispecific antibodies. In the same paragraph, Applicant described methods for the production of bispecific antibodies, which are known in the art. More specifically, Applicant stated on page 19 of the previously filed Amendment, "Such established techniques include chemical conjugation of two antibody molecules, fusion of two different hybridoma cell lines to create hybrid hybridomas, and genetic manipulation of recombinant molecules (Hayden et al. *Curr. Opin. Immun.* 9: 201-212 (1997))." The above statement evidences the fact that one of skill in the art could, at the time of Applicant's filing, use chemical conjugation of two antibody molecules, fusion of two different hybridoma cell lines to create hybridomas, and/or genetic manipulation of recombinant molecules to link the sequences of a β-amyloid antibody to an antibody to the transferrin receptor. Absent the teachings of Applicant's specification, one of skill in the art would not have been able to predict that the resulting fusion would be able to 1) bind β-amyloid and 2) cross the blood-brain barrier. It was not clear, prior to the teachings of Applicant's specification, that a bispecific antibody comprising a first antibody specificity which confers the ability of the bispecific antibody to cross the blood-brain barrier and a second antibody specificity conferring the ability of the bispecific antibody to bind to a β–amyloid epitope would have the stated properties.

Summary

In light of the above amendment, consideration of the subject patent application is respectfully requested. Any deficiency or overpayment should be charged or credited to Deposit Account No. 500282.

Respectfully submitted,



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Amendments to the Claims are reflected in the listing of claims which begin on page 3 of this paper.

Remarks/Arguments begin on page 17 of this paper.